IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff	)	C.A. No. 23-975 (RGA)
v.	)	**REDACTED - PUBLIC VERSION**
	)	Original filing date: February 26, 2024
LIQUIDIA TECHNOLOGIES, INC.,	)	Redacted filing date: March 4, 2024
Defendant.	)	

PLAINTIFF'S BRIEF IN SUPPORT OF
ITS MOTION FOR PRELIMINARY INJUNCTION

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INTRODUCTION

Liquidia Technologies, Inc. ("Liquidia") intends to launch its inhaled dry powder formulation of treprostinil, Yutrepia, for the treatment of pulmonary hypertension associated with interstitial lung disease ("PH-ILD") when United Therapeutics Corporation's ("UTC's") regulatory exclusivity expires on March 31, 2024. Liquidia makes these plans despite being enjoined by this Court from obtaining final approval for Yutrepia's original indication, pulmonary arterial hypertension ("PAH"), in a previous patent infringement suit brought by UTC. In fact, Liquidia has announced that it will launch Yutrepia for both PAH and PH-ILD as soon as it can, even though launching with a PH-ILD indication will infringe yet another UTC patent, U.S. Patent No. 11,826,327 ("the '327 patent"), and risks incurring damages Liquidia likely cannot pay. UTC offered to delay filing this Motion until 5 days after any decision relieving Liquidia from judgment in the prior litigation, provided that Liquidia would not launch Yutrepia for PH-ILD while UTC's Motion was pending in this action. Liquidia refused. Liquidia's hell or high water approach to launching its product for PH-ILD will irreparably harm UTC unless Liquidia is enjoined.

The facts readily satisfy the elements required for a preliminary injunction. *First*, Yutrepia infringes multiple claims of the '327 patent. Liquidia has no real non-infringement argument for many of these claims and Liquidia's invalidity and unenforceability challenges lack merit. *Second*, UTC would be irreparably harmed by Liquidia's launch in several ways—including lost market share and price erosion—harms that are irreversible, impossible to quantify with precision, and cannot be satisfied by Liquidia in any event. *Third*, the harm to UTC far outweighs any potential hardship to Liquidia from the status quo. *Fourth*, the public interest favors protecting valid patents and spurring innovation, and Liquidia's launch will not give patients additional material benefits.

UTC requests that the Court enjoin Liquidia from launching Yutrepia for treatment of PH-ILD pending a trial on the merits to preserve the status quo and prevent irreparable harm to UTC.

NATURE AND STAGE OF PROCEEDINGS

UTC asserts that Liquidia infringes the '327 patent. *See* D.I. 8; D.I. 17 at 2. Liquidia filed its Answer to the Amended Complaint and Counterclaims ("CC") on January 8, 2024. D.I. 12.

STATEMENT OF FACTS

I. UTC Has Developed Several Treatments For Pulmonary Hypertension

Pulmonary hypertension ("PH") is a life-threatening and often fatal disease characterized by elevated blood pressure in the lungs. There are different varieties of PH, including PAH and PH-ILD. Decl. of Steven Nathan, M.D. ("Nathan Decl.") ¶¶ 64–69. PH always involves elevated blood pressure, but the underlying causes, and thus treatments, vary. *Id.* And until recently, treprostinil treatments were approved for the treatment of only PAH (not PH-ILD). *Id.* ¶¶ 70–72.

UTC develops and commercializes products designed to address the needs of patients with chronic and life-threatening conditions, and the very reason for UTC's corporate creation was developing treatments for PH. Research continues, supported by sales of UTC's therapies for PH, including four treprostinil products: a bloodstream infusion (REMODULIN®), an extended-release tablet (ORENITRAM®), a nebulized inhaler (TYVASO®), and a dry powder inhaler (TYVASO DPI®). UTC's efforts to develop innovative treprostinil-based therapies led to multiple patents, including the '327 patent at issue, which expires on January 4, 2042. D.I. 8 ¶¶ 14–16.

The Food and Drug Administration ("FDA") approved TYVASO, the first inhaled treprostinil therapy, in 2009 for the treatment of PAH. *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1365 (Fed. Cir. 2023); D.I. 8 ¶¶ 2, 12-13. Then in 2021, following the INCREASE clinical trial sponsored by UTC, FDA approved TYVASO for the treatment of a new indication: PH-ILD. D.I. 8 ¶ 12. FDA granted UTC exclusivity for that new indication through March 31, 2024. *Id.* In 2022, FDA approved TYVASO DPI, the first commercialized dry powder inhaler ("DPI") version of treprostinil, for the treatment of both PAH and PH-ILD. *Id.* ¶ 13; CC

Ex. 3 §§ 1, 14.1, 14.3. Thus, UTC introduced not only the first inhaled treprostinil treatment, but also the first inhaled dry powder formulation, offering patients a smaller, more convenient device.

II. Liquidia Seeks To Launch A Follow-On PH Treatment

Liquidia seeks FDA approval to market a DPI version of treprostinil, called Yutrepia. Liquidia filed its original NDA in 2020 seeking approval for a PAH indication. Rather than conduct its own clinical trials, Liquidia relied on UTC's TYVASO product. Liquidia filed an amended NDA in late 2023 to add a PH-ILD indication that likewise relied on TYVASO.

III. Prior UTC and Liquidia Litigation

In 2020, UTC asserted that Liquidia and Yutrepia (then known as "LIQ861") would infringe several of UTC's patents. After a four-day trial, this Court found that "Liquidia's proposed LIQ861 product will induce infringement of claims 1, 4, 6, 7, and 8 of the '793 patent," making the effective date of final approval of Liquidia's NDA March 14, 2027. *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-cv-755, D.I. 436, ¶ 3-4 (D. Del. Sept. 9, 2022). Liquidia appealed and the Federal Circuit affirmed. *United Therapeutics*, 74 F.4th at 1360. Liquidia then petitioned for certiorari and moved in this Court for relief from judgment; the former was denied while the latter remains pending. No. 20-cv-755, D.I. 470. In parallel with the district court case, Liquidia sought *Inter Partes* Review ("IPR") of claims 1–8 of the '793 patent. *See Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2021-00406, 2022 WL 2820717 (P.T.A.B. July 19, 2022). Following a Final Written Decision finding the claims unpatentable, UTC appealed to the Federal Circuit, which affirmed. *United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 23-1805, 2023 WL 8794633 (Fed. Cir. Dec. 20, 2023). On January 19, UTC filed a petition for reconsideration and rehearing *en banc*, which remains pending. On February 16, 2024, the Federal Circuit asked Liquidia to respond to UTC's petition.

IV. Liquidia Seeks To Market Yutrepia Despite The '327 Patent

The '327 patent, granted November 28, 2023, covers a method of improving exercise capacity in PH-ILD patients through the administration of inhaled treprostinil. The Orange Book lists the '327 patent for TYVASO, the reference drug for Liquidia's NDA. On July 27, 2023, Liquidia announced it had submitted an amendment to its pending NDA to add the PH-ILD indication for Yutrepia. Flynn Ex. 1.[1] On December 12, 2023, Liquidia provided a certification asserting that the claims of the '327 patent were invalid or not infringed. Flynn Ex. 2, Notification Pursuant to § 505(b)(3)(B) of the Federal Food, Drug, & Cosmetic Act (21 U.S.C. § 355(b)(3)(B)(i)) and 21 C.F.R. § 314.52). Liquidia has undertaken substantial and meaningful preparation to launch Yutrepia immediately upon final approval, including "for both the PAH and PH-ILD indications as soon as possible." Flynn Ex. 1; D.I. 8 ¶ 29. Indeed, Liquidia has stated unequivocally that it intends to launch despite UTC's claims that it will infringe the '327 patent. Flynn Ex. 3 at 10 ("We're not going to hold back our launch for a patent that we think is invalid."). Liquidia's CEO suggested a reason for risking damages that Liquidia likely cannot pay: Liquidia needs to launch in PH-ILD to become profitable. *Id.* at 7 ("So we feel, and this is a critical aspect here, that if we're able to launch in both PAH and PH-ILD in April, that this funding will bridge us to profitability.").

ARGUMENT

Pursuant to 35 U.S.C. § 283 and Fed. R. Civ. P. 65, UTC respectfully requests the Court enjoin Liquidia from manufacturing, marketing, storing, importing, distributing, offering for sale, and/or selling Liquidia's Yutrepia product for PH-ILD in the United States pending trial. Liquidia has sought approval for both the PAH and PH-ILD indications, but UTC seeks only to enjoin

[1] The prefix "Flynn Ex." refers to exhibits attached to the concurrently-filed Declaration of Michael J. Flynn in Support of Plaintiff's Motion for Preliminary Injunction.

Liquidia from launching on PH-ILD, which will infringe the '327 patent and irreparably harm UTC in the process, irreversibly changing the market.[2] An injunction is needed to maintain the status quo. *AstraZeneca LP v. Apotex, Inc.*, 623 F. Supp. 2d 579, 614 (D.N.J. 2009).

To obtain preliminary injunctive relief, UTC must show "[1] that [it] is likely to succeed on the merits, [2] that [it] is likely to suffer irreparable harm in the absence of preliminary relief, [3] that the balance of equities tips in [its] favor, and [4] that an injunction is in the public interest." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1049 (Fed. Cir. 2010) (quoting *Winter v. Nat. Res. Def Council, Inc.*, 555 U.S. 7, 20 (2008)). No single factor is dispositive, as "[t]he weakness of the showing regarding one factor may be overborne by the strength of the others." *Belgium v. United States*, 452 F.3d 1289, 1293 (Fed. Cir. 2006) (quotation omitted).

Each factor weighs in UTC's favor. Accordingly, this Court should grant UTC's request for preliminary injunctive relief for Liquidia's planned infringement of the '327 patent.

I. UTC Is Likely To Succeed on the Merits

UTC will likely succeed on the merits because UTC will establish that Liquidia infringes at least claims 1, 6, 9-11, and 14 of the '327 patent,[3] and Liquidia cannot carry its burden on its invalidity and unenforceability challenges. *See AstraZeneca LP*, 633 F.3d at 1050.

A. UTC Is Likely To Succeed in Proving Infringement

UTC will readily show that Liquidia infringes claims of the '327 patent—indeed,

[2] FDA has tentatively approved Yutrepia for PAH. Liquidia has sought, but has not yet obtained, tentative approval from the FDA to market Yutrepia for PH-ILD. Liquidia has stated publicly that it intends to launch at risk with respect to the '327 patent and has not indicated that it expects to encounter any issues obtaining approval by April 1, 2024. Flynn Ex. 3 at 10; Flynn Ex. 4 at 1.

[3] For purposes of this Motion only, UTC asserts a subset of the '327 patent claims in order streamline proceedings. UTC reserves the right to assert any and all claims of the '327 patent against Liquidia as this litigation progresses. Similarly, UTC's responses to Liquidia's invalidity and unenforceability challenges to these claims are based on currently available knowledge, and UTC reserves the right to offer additional arguments and evidence as the case develops.

infringement of certain claims is largely undisputed. While UTC can show "it will likely prove infringement of one or more claims of the patents-in-suit" (*AstraZeneca LP*, 633 F.3d at 1050 (quotation omitted)), all that is required is a showing of a "reasonable probability of eventual success in the litigation." *Bennington Foods LLC v. St. Croix Renaissance, Grp.*, 528 F.3d 176, 179 (3d Cir. 2008). Liquidia infringed claims 1, 6, 9-11, and 14 of the '327 patent under 35 U.S.C. § 271(e)(2) when it filed its amendment adding PH-ILD as an indication. Moreover, if Liquidia is permitted to launch Yutrepia with a PH-ILD indication, use of Yutrepia in accordance with Liquidia's proposed label will directly infringe the asserted claims of the '327 patent, and Liquidia will be liable for inducing patients and healthcare providers to infringe. Liquidia does not appear to dispute that use of Yutrepia would directly infringe claims 1 and 6. CC ¶¶ 28–31; *see* Flynn Ex. 2 at 26. Liquidia's attempts to dispute infringement of the remaining asserted claims fall short.

1. Claim Construction

UTC is likely to succeed in proving that Liquidia infringes the claims of the '327 patent as properly construed. Claim 1 is the sole independent claim of the '327 patent and reads:

> A method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease, comprising administering by inhalation to the patient having pulmonary hypertension associated with interstitial lung disease an effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil or a pharmaceutically acceptable salt thereof in a single administration event that comprises at least 6 micrograms per breath.

The claim terms should be given their plain and ordinary meaning as understood by a person of ordinary skill in the art ("POSA"). *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). Here, the POSA would have a graduate degree in medicine or a field relating to drug development, such as an M.D. or a Ph.D., with at least two years' experience treating patients with interstitial lung disease, including PH-ILD. *See* Nathan Decl. ¶¶ 26–28.

Liquidia alleges that the preamble of claim 1—"[a] method of improving exercise capacity

in a patient having pulmonary hypertension associated with interstitial lung disease"—is limiting. *See* CC ¶ 28. Even assuming a POSA would read claim 1 in this way, UTC is likely to prevail.

2. The Use of Yutrepia Will Directly Infringe Claims 1, 6, 9-11 and 14 of the '327 Patent

When patients and healthcare providers use Yutrepia according to its proposed label (Flynn Ex. 2 at 9-11), claims 1, 6, 9-11, and 14 of the '327 patent will be directly infringed.

a. Independent Claim 1

Using Yutrepia according to its label will infringe claim 1. First, claim 1 recites a "method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease," and Liquidia instructs patients to use Yutrepia [redacted] Flynn Ex. 2 at 9. A POSA would understand [redacted] to be the same as "exercise capacity." Nathan Decl. ¶ 123. Second, Yutrepia will be "administered by inhalation" because the label states that [redacted] *Id.* ¶¶ 124–25; Flynn Ex. 2 at 10. Third, Yutrepia label recommends doses of [redacted], which is an "effective amount of at least 15 micrograms up to a maximum tolerated dose of treprostinil." Flynn Ex. 2 at 9–10; Nathan Decl. ¶¶ 126–34. Fourth, Yutrepia will be administered "in a single administration event that comprises at least 6 micrograms per breath." The label instructs that Yutrepia [redacted] Flynn Ex. 2 at 10; Nathan Decl. ¶¶ 135–38. Finally, Liquidia does not appear to dispute that claim 1 will be directly infringed when Yutrepia is used to improve exercise capacity in PH-ILD patients.

b. Dependent Claim 6

The use of Yutrepia will also infringe claim 6, which requires a statistically significant reduction in exacerbations of ILD. The Yutrepia label contains the same clinical trial data found

in the TYVASO label, *i.e.*, UTC's INCREASE study, in which patients receiving inhaled treprostinil showed a statistically significant reduction in ILD exacerbations versus those receiving placebo. Flynn Ex. 2 at 2; Nathan Decl. ¶¶ 91; 98; 139–41. By relying on UTC's INCREASE data, Liquidia has represented to the FDA, and defined its product, as one that will behave consistent with INCREASE's results. Because INCREASE showed a statistically significant reduction in exacerbations of ILD, Liquidia is liable for the same reduction by Yutrepia. *Id.*

c. Dependent Claims 9 and 10

The use of Yutrepia will meet each and every limitation of claims 9 and 10, which require an increase in the patient's forced vital capacity ("FVC") that is statistically significant (claim 9) or at least 20 mL (claim 10). Liquidia asserts that these claims will not be infringed because "the proposed label for Liquidia's Product does not provide any information regarding … FVC." CC at 30. However, the INCREASE study on which Yutrepia's label relies shows that patients experienced a statistically significant increase in FVC after both 8 and 16 weeks as required by claims 9 and 10. Nathan Decl. ¶ 91; 142–44. Thus, PH-ILD patients using Yutrepia according to its label to improve exercise capacity will practice the methods of claims 9 and 10. *Id.*; *see alsoOmega Pats., LLC v. CalAmp Corp.*, 920 F.3d 1337, 1344 (Fed. Cir. 2019).

d. Dependent Claims 11 and 14

The use of Yutrepia will meet each and every limitation of claims 11 and 14, which require that the method of claim 1 be performed using a pulsed inhalation device and dry powder inhaler, respectively. Yutrepia satisfies these claims because it [redacted] Ex NL at 9. Liquidia asserts that Yutrepia "does not utilize a 'pulsed inhalation device,'" CC ¶ 30, but a POSA would understand Liquidia's [redacted] to be a "pulsed inhalation device." Nathan Decl. ¶¶ 145–150. This is supported by the specification as well as claim 14, both of which describe a "dry powder inhaler" as a type of

"pulsed inhalation device." *Id.*; '327 patent at 21:6-14; Nathan Decl. ¶¶ 145–150.

3. Liquidia Will Induce Infringement of the '327 Patent

Liquidia will induce infringement of claims 1, 6, 9-11, and 14 of the '327 patent because it plans to market Yutrepia with a label that expressly directs patients and healthcare providers to use the product in a manner that infringes these claims. A drug label that encourages, recommends, or instructs users to perform a patented method—like Yutrepia's label—demonstrates intent to induce infringement. *See AstraZeneca*, 633 F.3d at 1060; *Sanofi v. Glenmark Pharms. Inc., USA*, 204 F. Supp. 3d 665, 673-74 (D. Del. 2016). Indeed, Liquidia admits to knowledge of the '327 patent (*see* Flynn Ex. 2 at 1), but nevertheless drafted its Yutrepia label to instruct end users administer Yutrepia according to a method that directly infringe that patent. Further, courts have found specific intent where even "some consumers" will inevitably practice the claimed methods. *AstraZeneca*, 633 F.3d at 1060; *Pernix (Ir.) Pain DAC v. Alvogen Malta Operations Ltd.*, 2018 WL 2225113, at *9 (D. Del. May 15, 2018). Here, Liquidia's label refers to clinical studies showing that patients taking Yutrepia will experience the benefits required by the asserted claims. UTC is therefore likely to succeed in demonstrating induced infringement.

B. UTC Will Likely Withstand Liquidia's Challenges on Validity and Enforceability of the '327 Patent

Liquidia challenges both the validity and the enforceability of the asserted claims. However, as discussed below, Liquidia will not be able to carry its burden on these challenges.

1. The Challenged Claims of the '327 Patent Are Valid

An issued patent is presumed valid, and an accused infringer must establish invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95, 102–03 (2011). At the preliminary injunction stage, the patentee need only show that the accused infringer is not "likely" to satisfy that exacting invalidity standard at trial. *AstraZeneca*, 633 F.3d at 1050, 1055.

Liquidia argues the asserted claims of the '327 patent are invalid for three reasons: (i) anticipation by the '793 patent; (ii) obviousness based on the '793 patent alone or in view of the 2009 package insert for TYVASO ("Tyvaso 2009 Label"), U.S. Patent Pub. No. 013/00966200 ("Wade '200"), and/or a journal article ("Parikh 2016"); and (iii) obvious type double-patenting based on the '793 patent. CC ¶¶ 17-23. Liquidia is unlikely to prove invalidity on any of the three grounds that it has asserted, particularly where the '793 patent, Tyvaso 2009 Label, Wade '200, and Parikh 2016 were considered or available to the examiner during prosecution. *See* Flynn Ex. 6 at 2; Flynn Ex. 7 at 90;*ee also Shire LLC v. Amneal Pharms., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015).

a. The Asserted Claims of the '327 Patent Are Not Anticipated.

Liquidia argues the asserted claims of the '327 patent are anticipated by the '793 patent. CC ¶¶ 17-20. These arguments fail because, even assuming the '793 patent is prior art to the '327 patent, the '793 patent does not disclose "each and every limitation" of the asserted claims, either expressly or inherently. *See Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014).

Liquidia asserts that the claims of the '327 patent "are limited to a 'method of improving exercise capacity in a patient having pulmonary hypertension associated with interstitial lung disease[.]'" CC ¶ 28 (quoting claim 1). However, the '793 patent does not teach administering inhaled treprostinil to improve exercise capacity and does not disclose any data regarding improved exercise capacity, let alone sufficient data to allow a POSA to practice the claim with the intent to improve exercise capacity. Instead, it describes only the hemodynamic effects of administering treprostinil. *See*, *e.g.*, '793 patent at 3:25-37; 8:57-62; 12:1-6; Nathan Decl. ¶¶ 175–80. The '793 patent also does not discuss other limitations (e.g., FVC) required by claims 6, 9–11 or 14 in the context of exercise capacity. *Id.* Liquidia attempts to fill this disclosure gap by arguing inherency, but that argument fails. Anticipation by inherency requires that the allegedly inherent attributes are the "necessary and inevitable consequence" of the alleged prior art disclosure under

normal conditions. *Glaxo Grp. Ltd. v. Teva Pharms. USA, Inc.*, 2004 WL 1875017, at *19 (D. Del. Aug. 20, 2004); *Rapoport v. Dement*, 254 F.3d 1053, 1058 (Fed. Cir. 2001). But not all patients treated in accordance with the '793 patent necessarily experience that improvement.

Liquidia cannot dispute that certain types of patients may benefit hemodynamically from inhaled treprostinil without also experiencing increased exercise capacity. Indeed, Liquidia has argued that administering inhaled treprostinil to so-called "Group 2" PH patients might cause more harm than good. *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 624 F. Supp. 3d 436, 466 (D. Del. 2022). As this Court found, those patients would experience a reduction in blood pressure, consistent with the claims of the '793 patent—but they would not necessarily experience an improvement in exercise capacity (which was not required by the '793 patent claims). *Id.* at 469. Likewise, the post-priority date INCREASE trial results described in the '327 specification show that not all PH-ILD patients necessarily and inevitably experience an improvement in exercise capacity; some patients even exhibited ***decreased*** exercise capacity. Nathan Decl. ¶¶ 175–80. The law is clear that "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Cont'l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991).

b. The Asserted Claims of the '327 Patent Are Not Invalid for Obviousness or Obviousness-Type Double Patenting

Liquidia argues that all asserted claims are invalid as obvious over the '793 patent alone and/or in combination with the Tyvaso 2009 Label, Wade '200, and/or Parikh 2016. CC ¶¶ 17–23. Liquidia also asserts the asserted claims are invalid for obviousness-type double patenting over the claims of the '793 patent. *Id.* ¶ 23. The main thrust of Liquidia's argument is that a POSA would (a) "be motivated to modify the disclosure of the '793 patent to treat PH-ILD patients in a manner to improve their exercise capacity," and (b) "have a reasonable expectation of success"

based on the data disclosed therein. *Id.* ¶ 21. Liquidia cannot prove either by clear and convincing evidence. *See Endo Pharms. Inc. v. Actavis LLC*, 922 F.3d 1365, 1373 (Fed. Cir. 2019).

As of the priority date of the '327 patent, the POSA would have known certain facts: (i) treprostinil was only approved for the treatment of PAH, one subset of PH; (ii) PH-ILD results from a different underlying cause than PAH; and (iii) no drug approved to treat PAH had ever shown efficacy in Group 3 PH patients in a randomized clinical trial—despite numerous failed attempts. Nathan Decl. ¶¶ 78–87; 207–12. Against that backdrop, while the POSA might understand that inhaled treprostinil as described in the '793 patent could provide hemodynamic benefit by reducing the elevated blood pressure that is the defining characteristic of PH, the POSA would have no reason to believe that using treprostinil would treat ILD and certainly no motivation to "modify the disclosure of the '793 patent" to improve exercise capacity in PH-ILD patients. CC at ¶ 21. Liquidia has not identified any part of the disclosed methods in the '793 patent that the POSA would modify—dose, breath count, route of administration, etc. Nor has Liquidia explained why the POSA would be motivated to modify the methods in the '793 patent to somehow improve exercise capacity (or any of the limitations in dependent claims 6, 9, and 10), or how or what alleged prior art disclosing the '327 patent's claimed benefits could be used to do so.

Liquidia also fails to explain why a POSA would be motivated to combine the '793 patent with any of the other asserted references. For example, neither Wade '200 nor the Tyvaso 2009 Label discloses an increase in exercise capacity of PH-ILD patients treated with treprostinil, nor does either teach that practicing the '793 patent would accomplish that increase. Nathan Decl. ¶¶ 196–212. Similarly, Parikh 2016 was a retrospective safety and tolerability study that disclosed limited efficacy data for the overall population of treated patients but said nothing about the particularized impact on PH-ILD patients. *Id.* Liquidia has pointed to nothing in the prior art that

would provide the motivation necessary to establish obviousness here.

Even if a POSA were motivated to administer treprostinil to PH-ILD patients as described in the '793 patent, they would not have had a reasonable expectation of success in achieving the claimed treatment methods. As mentioned above, numerous clinical trials seeking to apply PAH treatments to PH-ILD patients failed. There is nothing in either the '793 patent or the other cited references that would have given a POSA confidence that the particular doses of inhaled treprostinil disclosed in the '793 patent would be effective in improving exercise capacity in PH-ILD patients. *Id.* at ¶¶ 207–12. This is particularly true of the specific clinical endpoints required by the dependent claims, such as 6, 9, and 10. *Id.* Indeed, in the previous litigation before this Court regarding the '793 patent, Liquidia's expert, Dr. Hill, testified that hemodynamic improvements do *not* necessarily lead to clinical benefits. *See* Case No. 20-cv-755, D.I. 404 at 686:8–13 (Trial Tr. Day 3). Instead, a POSA would need clinical trial results to understand and know the effects of the '793 patent's methods on the exercise capacity of PH-ILD patients. Nathan Decl. ¶¶ 190–212; *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021). That UTC's groundbreaking INCREASE trial demonstrated improved exercise capacity in PH-ILD patients came as a surprise to many in the field, especially given the numerous prior failures discussed above. Nathan Decl. ¶ 214. It is only by impermissibly relying on hindsight that Liquidia can hope to establish a reasonable expectation of success.

Finally, objective indicia of non-obviousness, such as industry skepticism, unexpected results, unmet need, and failure of others all support the non-obviousness of the '327 patent. Nathan Decl. ¶¶ 213–17; *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012). Liquidia is therefore unlikely to prove that the claims of '327 patent are invalid for obviousness and/or obviousness-type double patenting.

2. The '327 Patent Is Enforceable

Liquidia's allegations of inequitable conduct, *see* CC ¶¶ 33–124, are littered with speculation but devoid of evidence. Both materiality and intent must be proven by clear and convincing evidence, *Therasense, Inc. v. Benton, Dickinson & Co.*, 649 F.3d 1279, 1287 (Fed. Cir. 2011) (en banc), and Liquidia cannot prove either.

a. Burying Claims Fail as a Matter of Law

Liquidia alleges that UTC engaged in inequitable conduct by "burying" certain information, including the '793 patent. These claims fail as a matter of law. "[A]n applicant cannot be guilty of inequitable conduct if the reference was cited to the examiner." *Jackson v. NuVasive, Inc.*, 2023 WL 6387866, at *3 (D. Del. Sept. 29, 2023) (quoting *Fiskars, Inc. v Hunt Mfg. Co.*, 221 F.3d 1318, 1327 (Fed. Cir. 2000)); *see also Symbol Techs., Inc. v. Aruba Networks, Inc.*, 609 F. Supp. 2d 353, 358 (D. Del. 2009) (same). Here, there can be no dispute that the '793 patent—which was disclosed in an IDS, considered by the Examiner, referenced many times in the file history (e.g., via the IPR petition UTC submitted), *and* is cited and incorporated by reference into the '327 patent specification—was before the examiner during prosecution. *See, e.g.*, Flynn Ex. 5 at 2; Flynn Ex. 6 at 2; 14; '327 patent, 20:56–57.

b. Liquidia Cannot Establish Materiality

Liquidia's pleading of inequitable conduct contains several muddled categories of allegations: (i) UTC buried the '793 patent and Liquidia's IPR petition for the '793 patent; (ii) UTC withheld certain references that purportedly describe the significance of the '793 patent; and (iii) UTC withheld Parikh 2016. CC ¶¶ 106–111. According to Liquidia, certain withheld references would have made clear to the Examiner that the '793 patent encompasses PH-ILD. CC ¶¶ 112; 120. Yet, as above, the Examiner was well aware of the '793 patent. The '793 patent discloses that "pulmonary hypertension" includes all five groups, something this Court confirmed

when it construed "treating pulmonary hypertension" as "treating all five Groups of PH." CC at 32 (citing CC Ex. 7 at 41). UTC cited Liquidia's petition for IPR of the '793 patent, a tome on the significance of the '793 patent in Liquidia's own words. Thus, the '793 patent was highlighted, not buried, and the additional documents concerning the '793 patent are cumulative, at best. Nathan Decl. ¶¶ 220–29; *see Therasense*, 649 F.3d at 1292 ("The materiality required to establish inequitable conduct is but-for materiality . . . prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art."); *Cal. Inst. of Tech. v. Broadcom Ltd.*, 25 F.4th 976, 991 (Fed. Cir. 2022) ("Prior art is not but-for material if it is merely cumulative."). Finally, none of these documents disclose improving exercise capacity in PH-ILD patients, and thus cannot be "but-for material." Nathan Decl. at ¶¶ 220–29.

Liquidia's reliance on Parikh 2016 fares little better. Like the '793 patent, the Examiner knew of this reference before he allowed the claims and thus it cannot be material. Flynn Ex. 7 at 90. Parikh 2016 is primarily focused on the safety and tolerability of high doses of treprostinil and only disclosed efficacy data averaged across the entire patient population. Nathan Decl. ¶¶ 230–34. Not only is this information not "but-for material" on its face, but it is also cumulative of several other clinical publications already before the Examiner. *Id.*

c. There Is No Evidence of Intent to Deceive

Liquidia offers specious allegations premised on "information and belief" and what the accused attorneys "knew or should have known" rather than evidence of malicious intent. *See, e.g.*, CC ¶¶ 92, 97-99, 103, 110, 114-117. For example, the only allegation Liquidia offers regarding Parikh 2016 is that the inventors and/or "UTC's legal department" would have reviewed it in an entirely different context over 4 years before the application issuing as the '327 patent was filed. *Id.* at ¶¶ 97-99, 103. Yet to prove intent, that "the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO" is insufficient. *Therasense*,

649 F.3d at 1290. Instead, Liquidia must establish that the single most reasonable inference able to be drawn from the evidence is that "the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Id.* Liquidia's speculative allegations of intent fall well short of this standard.

II. UTC Will Suffer Imminent, Irreparable Harm If an Injunction Is Not Entered

Liquidia's infringing launch of Yutrepia with a PH-ILD indication will result in irreparable harm to UTC that "no damages payment . . . could address." *Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012). "It is well-settled that, because the principal value of a patent is its statutory right to exclude, the nature of the patent grant weighs against holding that monetary damages will always suffice to make the patentee whole." *Hybritech Inc. v. Abbott Labs.*, 849 F.2d 1446, 1456–57 (Fed. Cir. 1988). Liquidia's launch will cause UTC irreparable harm in multiple other ways, including: (1) price erosion; (2) loss of sales and market share; (3) reduced research and development capabilities; and (4) loss of goodwill and first mover advantages. *See, e.g.*, *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 872-73 (Fed. Cir. 2017) (affirming irreparable harm findings based on lost sales, lost research and development, price erosion, and direct competition); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1381–82 (Fed. Cir. 2006) (affirming irreparable harm findings based on price erosion). Finally, even if any harms are compensable, Liquidia will likely be unable to approach anything close to full satisfaction monetary damages following judgment, making the injury irreparable.

First, Liquidia's entry in the PH-ILD market would cause lasting price erosion to UTC's TYVASO products. Declaration of Frederic Selck, Ph.D ("Selck Decl.") ¶¶ 16, 18, 63-76. [redacted] *Id.* ¶ 63. With multiple drugs available to treat the same condition, drug makers compete for formulary placement through price competition, including offering rebates or discounts to the

payor. *Id.* ¶¶ 64–65. Liquidia's launch of Yutrepia would result in payors demanding additional rebates or discounts from UTC for TYVASO products. [redacted]. *Id.* ¶¶ 65, 74. Even assuming some price erosion if Liquidia is able to launch for the PAH indication alone, the magnitude will be far greater and nearly impossible to quantity with precision if Liquidia is also allowed to launch on the infringing PH-ILD indication. *Id.* ¶¶ 16, 74. Following success at trial, UTC could not feasibly raise prices back to pre-Yutrepia levels, much less account for other competitive dynamics impacting the price in the intervening years. *Id.* ¶¶ 75, 113; *see Novartis Pharms. Corp. v. Accord Healthcare Inc.*, 2019 WL 2588450, at *5 (D. Del. June 24, 2019) (noting lack of ability "to raise the price back to where it is now, or to where it would have been" after trial). Indeed, if UTC tried to do so, it would likely "be widely criticized, thereby suffering irreparable harm to its goodwill." *Novartis*, 2019 WL 2588450, at *5; *see also Hoffmann-La Roche Inc. v. Cobalt Pharms. Inc.*, 2010 WL 4687839, at *12 (D.N.J. Nov. 10, 2010); Selck Decl. ¶ 16.

Second, Liquidia's entry into the market with a PH-ILD indication will significantly erode sales and market share for UTC's TYVASO products, making it "impossible to restore [UTC]'s . . . exclusive position by an award of damages and a permanent injunction." *Polymer Techs., Inc. v. Bridwell*, 103 F.3d 970, 975–76 (Fed. Cir. 1996); Selck Decl. ¶¶ 17, 86–95. If approved and launched, Yutrepia would directly compete with UTC's TYVASO products for PH-ILD patients at eroded prices, as those three products would be the only approved treatments in a relatively untapped and evolving market landscape. Selck Decl. ¶¶ 92, 112, 121. Such "[d]irect competition in the same market" place "strongly" suggests the existence of irreparable harm. *See, e.g.*, *Presidio Components, Inc. v. American Tech. Ceramics Corp.*, 702 F.3d 1351, 1363 (Fed.

Cir. 2012). Even if Yutrepia were later enjoined as to the PH-ILD indication, the injury would still be irreparable "because market share is so difficult to recover." *Fresenius Kabi USA, LLC v. Fera Pharms., LLC*, 2016 WL 5348866, at *13 (D.N.J. Sept. 23, 2016) (quotation omitted). Permitting Yutrepia's infringing launch on PH-ILD would tend to commoditize dry powder treprostinil products and reduce UTC's first mover advantages as the innovator due to Liquidia's early entry, significantly eroding its market share, sales, and brand recognition. Selck Decl. ¶¶ 19, 96–99. And if Liquidia were permitted to launch and later forced to withdraw, the improperly early access to the market would nevertheless increase its ability to market upon re-launch and have an impact on future prescriber decisions that would be difficult to quantify. Selck Decl. ¶ 91.

Third, Liquidia's premature market entrance would negatively impact UTC's research and development efforts. *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 872 (Fed. Cir. 2017) (affirming finding of irreparable harm based in part on lost R&D opportunity). UTC spends hundreds of millions of dollars on research and development, resulting in critical therapies such as REMODULIN, ORENITRAM, TYVASO, and TYVASO DPI—the first dry powder inhaled treatment for PH-ILD—but Liquidia's infringing launch would inhibit UTC's research and development, to UTC and patient detriment. *See* Selck Decl. ¶¶ 21, 100–02.

Fourth, Liquidia's launch will cause UTC to suffer irreparable harm due to "loss of goodwill [and] damage to reputation." *See Fresenius*, 2016 WL 5348866, at *13. UTC has spent significant resources building its TYVASO brand, and Liquidia is attempting to freeride on that goodwill by prematurely marketing a competing product that would inalterably impact UTC's reputation in the market. Selck Decl. ¶¶ 19, 103–04.

Fifth, even if some of UTC's damages are quantifiable, Liquidia is likely unable to pay UTC's potential monetary damages. Selck Decl. ¶ 20. Liquidia operates at a significant net loss,

and even were it to start generating revenue, an understated estimate of UTC's damages including from price erosion and lost sales, would be significantly higher than Liquidia's potential revenue. Selck Decl. ¶¶ 142–49. As such, the injury to UTC would be irreparable. *Eli Lilly & Co. v. Premo Pharm. Labs., Inc.*, 630 F.2d 120, 137 (3d Cir. 1980); *see also Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1155–56 (Fed. Cir. 2011).

Finally, there is no doubt that there is "some connection" between the harm alleged and the infringing acts. *Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1364 (Fed. Cir. 2013). The '327 patent is a method patent, and any Liquidia planned launch for PH-ILD will infringe the methods described. *See supra* § I; *see generally* Nathan Decl.; *see Janssen Prods., L.P. v. Lupin Ltd.*, 109 F. Supp. 3d 650, 700 (D.N.J. 2014) (finding causal nexus in patent process case).

In sum, the evidence is clear that UTC will suffer irreparable harm without an injunction.

III. The Balancing of Hardships Favors UTC

If Liquidia is not enjoined from launching Yutrepia with the PH-ILD indication, UTC will suffer severe and irreversible harm that outweighs any potential hardship for Liquidia. "In instances where the patent owner will suffer diminution in the value of its patent, the balance of hardships weighs in the owner's favor." *Everett Labs., Inc. v. Breckenridge Pharm., Inc.*, 573 F. Supp. 2d 855, 870 (D.N.J. 2008). UTC undertook significant and costly efforts to research, develop, patent, and commercialize TYVASO products and develop the PH-ILD market, and its total research and development spend from 2017-2022—which is in the billions—outstrips Liquidia's by at least an order of magnitude. *See* Selck Decl. ¶¶ 150–59. If Liquidia is not enjoined, UTC will lose the value of its '327 patent, which is not scheduled to expire until 2042. UTC may never restore its market share, product pricing or goodwill. *See supra* § II. By contrast, any harm that Liquidia might suffer from the injunction would be minimal. Liquidia would be "in the same position as it was before the injunction was granted." *See Impax Labs., Inc. v. Aventis*

Pharms., Inc., 235 F. Supp. 2d 390, 396 (D. Del. 2002). Any harm to Liquidia would be "the result of its own calculated risk to launch its product pre-judgment." *Sanofi-Synthelabo*, 470 F.3d at 1383. Further, UTC seeks to enjoin Liquidia from marketing Yutrepia only for PH-ILD; the requested injunction would not prevent a launch on any approved PAH indication.

IV. The Public Interest Favors Granting Preliminary Injunction

"[T]he public interest nearly always weighs in favor of protecting property rights," including the rights of valid patents like UTC's '327 patent here, as they encourage investment in bringing innovative products to market. *Evonik Degussa Gmbh v. Materia, Inc.*, 2017 WL 3434156, at *3 (D. Del. Aug. 10, 2017) (quotation omitted). The public interest in encouraging investment into drug development outweighs obtaining that same drug even via an infringing alternative—even if it were to some extent lower cost—when UTC's products meet the current market need. *See Eisai Co. v. Teva Pharms. USA, Inc.*, 2008 WL 1722098, at *12 (D.N.J. Mar. 28, 2008). UTC has been a leader in researching, developing, and bringing to market innovative therapies to treat PAH and PH-ILD, including TYVASO DPI, and patent rights are essential to preserving investments in research, development, and innovation. Selck Decl. ¶¶ 21, 150–57, 168–76. Liquidia's reliance on the abbreviated 505(b)(2) pathway piggybacks on UTC's TYVASO product associated research and development. Nathan Decl. ¶ 108. Without an injunction, the public interest "in protecting valid patent rights and in maintaining incentives for the massive investments required for drug development" would be destroyed. *See Novartis*, 2019 WL 2588450, at *9. Importantly, if an injunction is entered, PH-ILD patients will continue to have access to dry powder and nebulized treprostinil treatments. Selck Decl. ¶¶ 22, 164–67.

CONCLUSION

For the foregoing reasons, UTC respectfully requests that the Court grant UTC's Motion for a Preliminary Injunction and enter the Proposed Order.

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CERTIFICATE OF SERVICE

I hereby certify that on February 26, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on February 26, 2024, upon the following in the manner indicated:

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